oncogene as compared to the corresponding wild-type AAV Rep78 (SEQ ID N:6). Applicant did not amend "a truncated" to "the truncated" as the language of claim 7 is clearer if "a truncated" is used. Applicant believes that these amendments have overcome the Examiner's objections and withdrawal of this rejection is requested.

Claims 4 and 5 are rejected as indefinite regarding the recitation of no- and weak-binding. The Examiner has suggested language to overcome this rejection and applicants have amended these claims as requested by the Examiner. Applicant does not believe that these amendments further limit the claims as compared to the previous language. Withdrawal of this rejection is requested.

Claims 13 and 46 are rejected as being indefinite regarding claiming that binding results in AAV DNA replication and/or AAV virion production. These claims have been amended to overcome these specific issues. This phrase has been deleted in claim 13 and additional clarifying language has been added to claim 46.

In view of the above comments and amendments to clarify the invention and not to limit it, it is requested that these rejections be withdrawn with regard to rejected claims.

Rejections under 35 U.S.C. § 112, first paragraph

Claim 20

Claim 20 is rejected by the Examiner as allegedly only being enabled for the *in vitro* administration of the AAV Rep78 mutant for replication studies and it not enabled for *in vivo* therapeutic uses. The Examiner recites the factors in *Ex parte Forman* to support his position that claim 20 is not enabled.

Claim 20 has been amended to recite that the AAV Rep78 mutant binds to "at least one DNA sequence obtained from a papillomavirus" and that the mutant's DNA binding is enhanced as compared to the binding of the corresponding wild-type AAV Rep78 protein as set forth in SEQ ID NO:6 to the DNA sequence. Thus, this claim focuses on the AAV Rep78 mutants that bind to papillomavirus DNA and not on HIV or other cancers. Applicant submits that this amendment addresses the major issue in the Examiner's rejection.

In support of this claimed method, applicants herewith provide a declaration by Dr. Paul Hermonat, the inventor of the present application, in which he discusses data in the

attached Coker *et al.* publication to show that AAV containing the wild-type Rep78 protein inhibits papillomaviruses. Further, the Coker *et al.* publication discloses in the "INTRODUCTION" that AAV is able to inhibit papillomavirus oncogene expression, papillomavirus-mediated transformation and papillomavirus replication. As commented on in the last sentence on page 83, second column of Coker *et al.*, these inhibitory effects have been mapped to the AAV Rep78 protein. Dr. Hermonat's declaration also provides additional publications that are cited in Coker *et al.* For the Examiner's convenience, the 1994b Hermonat publication and the Horer *et al.* publication discussed, in Coker *et al.* and in Dr. Hermonat's declaration, are the same publications also cited in the IDS submitted on July 13, 2002 as A7 and A13, respectively.

Additionally, Dr. Hermonat comments on the *in vitro* data presented in the present application supports that the disclosed novel AAV Rep78 mutants, such as the AAV Rep-192^{HG}, bind more strongly to specific DNAs as compared to the wild-type Rep78 protein. These stronger DNA binders are identified as useful for treating cancer. See the specification, page 26, lines 19-22. Therefore, in view of the claim amendments to claim 20, the fact that the novel AAV Rep78 mutants possess enhanced binding to papillomavirus DNA as compared to the wild-type AAV Rep78 protein, Dr. Hermonat's declaration that discussing Coker *et al.* and cited prior art and the results in the specification, applicant submits that claim 20 is enabled. It is requested that this rejection be withdrawn.

Claim 11

Claim 11 is rejected as not being enabled. Claim 11 is directed to AAV Rep-77^{LG} and AAV Rep-64^{LH} 65^{TM}. However, the examiner states that the specification lacks complete deposit information for the deposit of AAV Rep-77^{LG}, AAV Rep-79^{FA} and AAV Rep-192^{HG}.

Applicant respectfully disagrees with the Examiner's that a deposit is necessary. Applicants have provided the complete nucleic acid and amino acid sequences for the AAV Rep78 protein. The MPEP in §2402 states that

> Every patent must contain a written description of the invention sufficient to enable a person skilled in the art to which the invention pertains to make and use the invention.

Further, MPEP 2404 reciting 37 CFR 1.802 (b) states that

> (b) Biological material need not be deposited unless access to such material is necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112. ... Biological material need not be deposited, *inter alia*, if it is known and readily available to the public or can be made or isolated without undue experimentation.

All of the AAV Rep78 mutants can be prepared from the wild-type AAV Rep78 protein. Figure 15A-C discloses the nucleotide sequence encoding AAV Rep78 as nucleotides 321-2186 and Figure 16 provides the corresponding amino acid sequence of the AAV Rep78 protein. Thus, the specification provides the sequences needed to prepare the AAV Rep78 mutants. The disclosure of these sequences in the specification make them known to the skilled person who can prepare his own sequences via known methods of DNA or amino acid synthesis. Applicant submits that knowing the AAV Rep78 protein nucleic acid and amino acid sequences, a person skilled in the art can follow the specification using standard experimentation to modify a known amino acid sequence/nucleotide sequence, to prepare the mutants with the desired modifications from the wild-type AAV Rep78 nucleic acid and amino acid sequences. See the specification on page 19, lines 15 to page 20, line 13. The last line of this portion of the specification recites the following:

> To insure that the mutations were transferred into the full length AAV background, the region of the mutation was once again sequenced as described above.

Applicant notes that the Examiner admitted in a previous Office Action that the specification does provide guidance as to how to AAV Rep 77^{LG} and that this information can be used to make AAV Rep 79^{FA} and 192^{HG} modified proteins. Therefore, if AAV Rep 77^{LG} can be used to make the other two modified proteins then it also can be utilized to make other AAV Rep 78 mutants. The amino acid and nucleic acid sequences of AAV Rep 78, methods of making the AAV Rep mutants and methods for assaying for their binding is disclosed in the present application and it would not require undue experimentation to make other AAV Rep 78 modified proteins.

Further, the specification discloses assays for the assessing binding activity of the modified proteins to known binding partners, which does not require undue experimentation. It only requires following the methods provided in the specification to prepare the exemplified AAV Rep 78 mutants by performing standard experimental methods known to persons skilled in the art. Additionally, the examples provided in the present specification to

prepare AAV Rep 77^{LG}, 79^{FA}, and 192^{HG} modified proteins can be used to prepare other mutants proteins.

As argued above, the amino acid and nucleic acid sequences are known and provided in the specification, figures and Sequence Listing. Plasmids containing a specific AAV Rep 78 mutant can be prepared using different mutagenic oligonucleotides. All of the manipulations to create other mutant proteins from known sequences are well within the skill of the artisan. Thus, a person of skill in the art would be able to determine through standard trial and error experimentation other AAV Rep 78 proteins using the guidance in the specification for making AAV Rep 77^{LG}, 79^{FA}, and 192^{HG} modified proteins.

Applicant submits that a deposit it not necessary as the nucleic acid and amino acid sequences are disclosed. It is requested that this rejection be withdrawn.

CONCLUSION

The present response is intended to be a complete response to the Examiner's Office Action. It is believed that the above arguments and amendments to the claims place the application in condition for allowance, and a notice to that effect is respectfully requested. If there are any minor issues which can be taken care by telephone, it is requested that the Examiner contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

Date July 11, 2003

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Marked-Up Copy of Claims:

2. (Amended) An adeno-associated virus (AAV) Rep78 mutant comprising an AAV Rep78 modified protein that binds to at least one DNA sequence obtained from one or more of a papillomavirus, an AAV, an oncogene or a HIV differently as compared to the binding of the corresponding wild-type AAV Rep78 protein as set forth in SEQ ID NO:6 **to said DNA sequence**, wherein said different DNA binding is selected from the group consisting of no DNA binding, weak DNA binding and enhanced DNA binding as compared to the binding of said wild-type AAV Rep78 protein.

4. (Amended) The AAV Rep78 mutant of claim 2, wherein said AAV Rep78 modified protein having no DNA binding or weak DNA binding to said DNA sequence obtained from at least one of a papillomavirus, an AAV, an oncogene or a HIV [that]**, and wherein the no DNA binding or weak DNA binding** results in the generation of higher levels of AAV DNA replication and virion numbers **compared to the corresponding wild type AAV Rep78 protein**.

5. (Amended) The AAV Rep78 mutant of claim 2, wherein said AAV Rep78 modified protein having enhanced DNA binding to said DNA sequence obtained from at least one of a papillomavirus or an oncogene [that]**, and wherein the enhanced DNA binding** results in enhanced inhibition of at least one of a papillomavirus or an oncoprotein **compared to the corresponding wild type AAV Rep78 protein**.

7. (Amended) The AAV Rep78 mutant of claim 6, wherein said AAV Rep78 modified protein is a truncated AAV Rep78 protein [containing at least the minimum number of amino acids of the wild-type AAV Rep78 protein necessary to bind] **that binds** to said DNA sequence**, and wherein said binding results in** [to obtain] enhanced inhibition of a papillomavirus or an oncogene **compared to the corresponding wild-type AAV Rep78 protein**.

13. (Amended) A fusion protein comprising an AAV Rep78 modified protein that binds to at least one DNA sequence obtained from one or more of a papillomavirus, an AAV, an oncogene or a HIV differently as compared to the binding of the corresponding wild-type

AAV Rep78 protein as set forth in SEQ ID NO:6, and [that results in AAV DNA replication and/or AAV virion production,] wherein said different DNA binding is selected from the group consisting of no DNA binding, weak DNA binding and enhanced DNA binding as compared to the binding of said wild-type AAV Rep78 protein.

19. (Amended) A pharmaceutical composition comprising at least one AAV Rep78 mutant according to claim 2 **in admixture** with a pharmaceutically acceptable carrier.

20. (Amended) A method of treating papillomavirus associated diseases or cancer comprising administering [said] **a** pharmaceutical composition [of claim 19] **comprising at least one adeno-associated virus (AAV) Rep78 mutant in admixture with a pharmaceutically acceptable carrier to a patient afflicted with a papillomavirus associated disease or cancer, wherein said mutant comprises an AAV Rep78 modified protein that binds to at least one DNA sequence obtained from a papillomavirus, wherein said DNA binding is enhanced DNA binding as compared to the binding of the corresponding wild-type AAV Rep78 protein as set forth in SEQ ID NO:6 to the DNA sequence** [to a patient afflicted with a papillomavirus associated disease or cancer].

46. (Amended) The AAV Rep78 mutant of claim 2, wherein said **no DNA binding or weak DNA** binding results in **the generation of higher levels of** AAV DNA replication and/or AAV virion production **compared to the corresponding wild type AAV Rep78 protein**.